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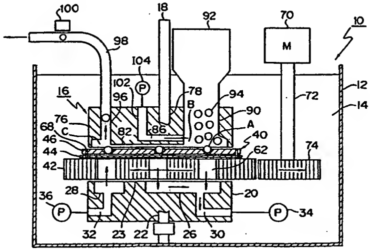

(57) Abstract

A separator (10, 110) for separating each bead (94, 134) from a group of beads (94, 134) includes a bead holder (46, 116). The bead holder (46, 116) has a surface having a recess (58, 64, 132) sized to receive a single bead (94, 134), a passage (130) connected at its one end to the recess (58, 64, 132), and a restricting portion for preventing the bead (94, 134) from entering into the passage (130). The separator (110) further includes first (A), second (B), and third (C) stations. The first station (A) is to introduce a negative pressure in the passage (130), thereby holding the bead (94, 134) in the recess (58, 64, 132). The second station (B) is to eject a liquid (14, 174) around the recess (58, 64, 132) retaining the bead (94, 134), thereby removing a bead (94, 134) or beads possibly existing around the recess (58, 64, 132) away from the recess (58, 64, 132). The third station (C) is to introduce a positive pressure in the passage (130), thereby releasing the bead (94, 134) from the recess (58, 64, 132). In addition, a transporting means (70, 124) is provided for advancing the recess (58, 64, 132) through first (A), second (B), and then third (C) stations.

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DESCRIPTION

APPARATUS AND METHOD FOR SEPARATING AND SUPPLYING SINGLE BEADS FROM A GROUP OF BEADS FOR USE IN COMBINATORIAL SYNTHESIS PROCESS

TITLE OF THE INVENTION

The present invention relates to an apparatus for separating and then supplying a bead having a diameter of about 0.05 to 0.5mm, for example, from a group of such beads. In particular, the present invention relates to a bead separator, preferably for use in a combinatorial synthesizing process in which a variety of compounds are effectively synthesized and/or in a high throughput process in which a variety of compounds are effectively screened off.

BACKGROUND OF THE INVENTION

Typically, in the process for developing a new medicine, a great number of compounds must be synthesized and then evaluated in bio-activities thereof. In addition, the synthesization of the compounds needs to be performed effectively in a short period of time. For these reasons, a combinatorial synthesizing method and a high throughput cleaning method have been spotlighted in recent years.

For the combinatorial synthesizing method, a so-called solid phase synthesizing method has been appropriately employed. The solid phase synthesizing method is characterized in that used as a bearing member is a small bead made of synthetic resin. Generally, the bead has a diameter of about 0.05 to 0.5mm. Each compound is synthesized on the small resin bead. Then, the synthesized compound is separated from the bead and, thereby, obtained independently. With the method, a number of compounds are effectively synthesized and then obtained.

The solid phase combinatorial synthesizing method using small beads is generally classified into a split mixing method and a parallel method. In the parallel method, all beads are subjected to a plurality of reaction processes and then accommodated in the final reaction chamber. Therefore, the beads have the same reaction history. This means that a single compound is separated and then obtained from the beads. In the split mixing method, on the other hand, the beads in the final reaction chamber have different reaction histories. Therefore, separating compounds from associated beads in a group will result in a mixture of various compounds. As a result, at screening, it is not preferable for a number of compounds to be processed in terms of the resultant precision of the experiment as well as the fixing of the active compounds.

For the reason, some improvements are needed in an assembling process or in another process prior to the assembling process of the split mixing method. Specifically, there has been proposed two methods. One method has the steps of assembling beads each bearing compounds, selecting beads representing some activities, separating beads from associated compounds, and determining the structures of the compounds. The other method has the steps of chemically or electrically conjugating beads with a mark or tag, and determining the structures of the compounds. The former method, because the assembling being performed on the solid phase, is subjected to various restrictions, thereby lacking in the universality. The latter method, on the other hand, requires a special technique and a device for providing tags on the beads.

Under the circumstances, the inventors of the present invention have been conceived a process for distributing a certain number of beads to each well of micro-tighter plate. With the new method, since each bead is permitted to bear only one compound, various types of compounds, corresponding to respective beads, can be obtained in each well.

On the other hand, to this purpose for distributing one or more beads to each well, there have been proposed a nozzle distribution method and a tube

distribution method. In the nozzle distribution method, each bead is picked up and held at an end opening of a nozzle or tubule smaller in diameter than the beads by the suction introduced in the nozzle and then carried to the well. On the other hand, in the tube distribution method, provided is a suspension that is a mixture of beads and a liquid having the same density as the bead, and each bead is drawn with the liquid through a tubule having a diameter slightly larger than the beads.

However, with the nozzle distribution method, the beads can be damaged when they are sucked at the end of the nozzle. Also, it is difficult to confirm whether the bead has been held at the end of the nozzle, rendering the method unreliable. Further, for both methods, a probability for picking up beads, or the number of beads to be picked up by the nozzle or tubule, depends upon the number of beads included in the suspension, which makes the beads supplying methods less reliable.

SUMMARY OF THE INVENTION

To overcome above-described drawbacks in the conventional bead separators, a bead separator of the present invention includes a bead holder. The bead holder has a surface having a recess sized to receive a single bead, a passage connected at one end thereof to the recess,

and a restricting portion for preventing the bead from being entering into the passage. Also, the bead separator has first, second, and third stations. The first station is to introduce a negative pressure in the passage, thereby holding the bead in the recess. The second station is to eject a liquid around the recess retaining the bead, thereby removing a bead or beads possibly existing around the recess away from the recess. The third station is to introduce a positive pressure in the passage, thereby releasing the bead from the recess. A transporting means is provided for moving the recess through the first, second, and then third stations.

In another aspect of the present invention, the recess is in the form of truncated cone having a first opening away from the passage and a second opening adjacent to the passage. The second opening is sized to be smaller in diameter than the bead to form the restricting portion.

In another aspect of the present invention, the recess is in the form of cylinder. The bead holder further comprises a filter positioned between the recess and the passage for preventing the bead from entering into the passage.

In another aspect of the present invention, the recess has a depth smaller than a size of the bead so that a portion of the bead protrudes from the recess.

In another aspect of the present invention, the separator further includes a member that has a groove extending adjacent to a pass along which the recess moves past the second to third stations. The groove has a depth smaller than a size of the bead so that the protruded portion of the bead moves in the groove.

In another aspect of the present invention, the bead holder and the first to third stations are substantially immersed in the liquid.

Another separator for separating each bead from a group of beads includes an axis, a bead holder rotatably mounted about the axis. The bead holder has a recess sized to receive a single bead, a passage fluidly connected to the recess, and a restricting portion for preventing the bead from entering into the passage. Further, the separator has a motor for rotating the bead separator about the axis so that the recess of the bead separator moves along a circular pass. A first station provided adjacent to the circular pass has a first chamber for receiving the group of beads and means for introducing a negative pressure in the passage when the recess is moving past the first station and, thereby, holding the bead in the recess. A second station provided adjacent to the circular pass and subsequent to the first station has means for keeping the negative pressure in the passage and a nozzle for ejecting

a fluid adjacent to the recess and, thereby, removing a bead or beads possibly existing around the recess away from the recess. A third station positioned subsequent to the second station and adjacent to the circular pass, the third station has means for introducing a positive pressure in the passage for releasing the bead from the recess.

A method for separating each bead from a group of beads preferably of the present invention has the steps of:
providing a bead holder having a recess sized to receive a single bead, a passage fluidly connected with the recess, and a restricting portion for preventing the bead from entering into the passage;
introducing a negative pressure in the passage, thereby receiving the bead in the recess;
ejecting a liquid around the recess retaining the single, thereby removing a bead or beads possibly existing around the recess away from the recess;
introducing a positive pressure in the passage, thereby releasing the bead from the recess.

With the separator of the present invention, each bead is positively separated from its group and then received in the truncated or cylindrical recess without any damages. Then, the separated bead is transported to a well of the combinatorial synthesizing method, for example.

Also, the bead or beads existing around the

recess are removed from the recess at the second station, which ensures that only one bead is separated from its group and then transported to the next process.

Further, the groove formed from the second to third stations prevents the bead from being damaged.

Furthermore, in the event that the bead holder and the stations are immersed in the liquid, the beads are prevented from attracting each other by an electric charge generated by the mutual contact and/or by adhesiveness thereof. This ensures that each bead is separated from its group.

Moreover, it is not necessary for the specific density of the liquid to be adjusted to that of the bead, unlike the conventional nozzle distribution method and tube distribution method.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic cross-sectional view of a bead separator of a first embodiment according to the present invention;

Fig. 2 is an exploded perspective view of a separation unit of the bead separator shown in Fig. 1;

Fig. 3 is a schematic enlarged cross-sectional view showing beads being transported form a restricting station and to a release station in the bead separator

shown in Fig. 1;

Fig. 4 is a schematic cross-sectional view of another bead separator of a second embodiment according to the present invention; and

Fig. 5 is a cross-sectional view taken along a line V-V shown in Fig. 4.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

With reference to the drawings, in particular in Fig. 1, there is illustrated a separator or bead separator generally indicated by reference numeral 10. The separator 10 has a container or vessel 12 having a specific transporting medium or liquid 14 such as ethanol. A group of small beads, each bead having a specific density slightly greater than that of the liquid 14, are also provided in the vessel 12 for a combinatorial synthesizing process. A separation unit 16 is provided in the liquid 14 for separating each bead from its group one by one.

Referring in detail to Fig. 2, the separation unit 16 includes a shaft 18 extending substantially vertically. Instead, the shaft 18 may be slanted against the vertical axis. A lower plate 20 in the form of disc has a central hole 22 into which the lower end of the shaft 18 is securely inserted. The lower plate 20 has an upper surface 23 extending perpendicular to the shaft 18. The

upper surface 23 is formed with an elongated groove 26 and a shortened groove 28, both extending along an imaginary circle 24 of certain diameter having its center on the shaft 18. The lower plate 20 includes another two holes, 30 and 32. One end of the hole 30 is connected to the elongated groove 26 at the upper surface 23 and the other end to an inlet of a suction pump 34. On the other hand, one end of the hole 32 is connected to the shortened groove 28 at the upper surface 23 and the other end with an outlet of a supply pump 36. An outlet of the suction pump 34 and an inlet of the supply pump 36 are also positioned in the liquid 14 in the vessel 12 or in another reservoir not shown.

A rotary unit 40, which is positioned on the upper surface 23 of the plate 20, includes three discs; gear plate 42, screen or filter 44, and beads holder 46. The gear plate 42 is formed with a hole 48 at its center and a gear 50 at its outer periphery. Also, the gear plate 42 is formed with six holes 52 about the hole 48 at regular angles of 60° on an imaginary circle having the same diameter as the imaginary circle 24. The number and angle of the holes are not limited thereto, and may be changed as necessary.

The filter 44 is selected from filtering members, each of which capable of preventing the beads each having a

diameter of about 0.05 to 0.5mm from passing through the member. In this embodiment, the filter is made from a metal screen having a mesh size of 0.005mm. The filter 44 is formed at its center with a hole 54 so that the shaft 14 can be inserted therein.

The beads holder 46, which is made from a plate having a thickness (e.g., 0.2mm) similar to or less than the size of the bead, is formed at its center with a hole 56 so that that the shaft 14 can be inserted therein. Also, the beads holder 46 is formed with six holes or recesses 58 at regular intervals about the hole 56 on an imaginary circle having the same diameter of the imaginary circle 24. As best shown in Fig. 3, each recess 58 is in the form of truncated cone and communicates between upper and lower surfaces, 60 and 62, of the holder 46. Preferably, an upper opening of the recess 64 adjacent to the upper surface 60 has a diameter of about 0.4mm, for example, which is greater than the bead size. a lower opening of the recess 64 adjacent to the lower surface 62, on the other hand, has a diameter of about 0.2mm, for example, which is smaller than the bead size.

The gear plate 42, filter 44, and beads holder 46 are assembled into the rotary unit 40. Specifically, the three members 42, 44, and 46 are mounted one on top the other so that the central holes 48, 54, and 56 are aligned

in a line. Simultaneously, the holes 52 of the gear plate 42 and the recesses 58 of the beads holder 46 are aligned that each hole 52 and recess 58 are communicated with each other through the filter 44. Then, the three elements are secured with a suitable glue or fixing means such as bolts and nuts 68. Thereafter, the shaft 18 is passed through the aligned holes 48, 54, and 56 and positioned for rotation about the shaft 18 on the bottom plate 20 so that the lower surface of the gear plate 42 makes a contact with the lower plate 20.

To rotate the rotary unit 40, the separator 10 includes a motor 70 fixed on the vessel 12 through a support not shown. The motor 70 has an output shaft 72 on which a gear 74 is fixed. The gear 74 is engaged with the peripheral gear 50 of the gear plate 42. This allows that upon rotation of the motor 70 the rotary unit 40 rotates in the direction indicated by an arrow 75 at a rotational speed of about 5rpm, for example.

Referring to Figs. 1 and 2, the shaft 18 also supports an upper plate 76 positioned adjacent to the rotary unit 40 but away from the lower plate 20. The upper plate 76 is formed with a hole in which the shaft 18 can be inserted. To clarify, the hole 78 is eliminated from Fig. 2 and in part from Fig. 1. Also, the upper plate 76 is formed at its lower surface 80 with a groove or tunnel 82

about the hole 78. The tunnel 82 extends along an imaginary circle having the same diameter as the imaginary circle 24. Also, a depth of the tunnel 82 is dimensioned to be lower than the bead size.

As best shown in Fig. 2, an extended concave portion or bead supply chamber 84 having a width greater than the groove 82 is formed in the lower surface 80, adjacent to the tunnel 84, so that it is connected with one end of the tunnel 82. Also, another groove 86 is formed in parallel to and outside the tunnel 82 so that one end thereof is connected with the chamber 84 in the vicinity of the one end of the tunnel 82 connected to the chamber 84. In Fig. 1, the groove 86 is illustrated above the tunnel 82 to show both groove 86 and the tunnel 82, though; it is of course formed in the lower surface of the upper plate 76.

In addition, the upper plate 76 is formed with a hole or bead supply hole 90 extending from the lower and upper surfaces, 80 and 88, of the plate 76. In particular, the lower opening of the hole 90 is connected to an intermediate portion of the recess 84 and the upper opening thereof to a reservoir or hopper 92. (see Fig. 1) The hopper 92 is designed that it can accommodates a number of beads 94 made of styrene resin, for example, each having a diameter of about 0.05 to 0.5mm, and the liquid 14.

Further, the upper plate 76 is formed with a bead

passage 96 having an inner diameter of slightly greater than the bead and extending between the lower and upper surfaces, 80 and 88. Also, the lower opening of the passage 96 is connected to the opposite end of the tunnel 82 away from one end thereof to which the extended chamber 84 is connected. On the other hand, the upper opening of the passage 96 is connected to a bead transporting tube 98 having an inner diameter slightly greater than the bead. The bead transporting tube 98 is equipped with an optical bead detector 100 for detecting bead being transported in the tube.

Furthermore, the upper plate 76 is formed with a liquid supplying passage 102. The lower opening of the passage 102 is connected to the opposite end of the groove 86 away from one end of thereof to which the extended chamber 84 is connected. On the other hand, the upper opening of the passage 102 is connected to an outlet (not shown) of a pump 104. An inlet of the pump 104 is positioned in the liquid 14 for supplying the liquid 14 into the passage 102.

The upper plate 76 so constructed is fixedly mounted around the shaft 18 with the shaft inserted in the central hole 78 and on the bead holder 46 so that the lower surface 80 of the plate 76 contacts slightly with the upper surface 60 of the bead holder 46. Also, the lower opening

of the passage 96 is faced to one end of the shortened groove 28 of the bottom plate 20, positioned downstream side of the rotational direction 75 and away from the elongated groove 24.

Operations of the separator 10 so constructed for separating each bead 94 from the group of the beads will be described. The group of beads from which each bead will be separated is supplied to the bead hopper 92 with the liquid 14. The beads 94, since each having a specific density greater than that of the liquid in this embodiment, move down into the hole 90 and then into the chamber 84 (i.e., retaining station A), rather than floating on the surface of the liquid 14.

The rotation of the motor 70 is transmitted through the output shaft 72 and gear 74 to the gear plate 42, thereby rotating the rotary unit 40 in the direction indicated by the arrow 75. This allows the recesses 58 in the bead holder 46 to pass by the chamber 84 according to the rotation of the bead holder 46.

Each recess 58 when confronting to the chamber 84 is supplied in its upper opening 64 with one bead 94. It should be noted that the, since the thickness of the bead holder 46 is almost identical to or less than the bead size and the inner diameter of the top opening 64 is slightly greater than the bead size, each recess 58 receives only

one bead 94. (see Fig. 3)

By driving the pump 34, a flow of the fluid 14 is formed through chamber the chamber 84, associated recesses 58, filter 44, associated passages 52, elongated groove 26, and passage 30. Due to this, the bead 94 is held in the recess 58 passing by the chamber 84. For this purpose, the pump 34 is preferably controlled to feed the liquid at about 0.1 ml per minute.

In addition, the liquid 14 is fed from the pump 104 through the passage 102 and then groove 86 into the bead supply chamber 84 in the vicinity of the entrance of the tunnel 82, i.e., a restricting station B, located on the downstream end of the bead supply chamber 84 with respect to the rotational direction indicated by the arrow 75. Thereby, bead or beads possibly retained in the vicinity of the recess 58 are removed away from the recess 58 in the direction opposite to the arrow 75 when the recess 58 moves past the restricting station B. For this purpose, the pump 104 is preferably controlled to feed the liquid at about 12ml per minute.

The bead 94 retained in the recess 58 enters and moves along tunnel 82 in the upper plate 76 by the rotation of the rotary unit 40. Then, the bead 94 as well as the recess 58 reaches a release station C where the shortened groove 28 opposes to the passage 96. In the release

station C, another flow of liquid 14 generated by the supply pump 36 through the passages 32 and then 96. Due to this liquid flow, once the recess 58 with bead 94 has reached the release station C, the bead 94 is released out of the recess 58 into the passage 96. To this end, the pump 36 is preferably controlled to feed the liquid at about 0.5ml per minute.

Afterwards, the bead 94 is transported by the liquid flow into the bead transporting tube 98 where it is detected by the bead detector 100. When the bead detector 100 has detected the bead 94, it transmits an electric signal to a bead distributor not shown where the bead is distributed into a specific well in the combinatorial synthesizing process.

It should be noted that the bead size is not limited to the size above-mentioned, and the present invention is applicable to any size of beads. Therefore, it is to be understood that each size of the elements and portions can be changed in accordance with the bead size within the scope of the claims of the present invention.

For example, in the previous embodiment, the bead, holder is in the form of disc and supported for rotation, so that the recesses formed therein moves along the circular pass. Instead, it may be envisioned that bead holder takes another configuration, such as rectangular.

Further, it may be envisioned that the bead holder travels along a rectangular pass on which the stations A to C are positioned.

Also, in the previous embodiment, the separation unit is fully immersed in the liquid. This is advantageous that no air is drawn into the bead transporting passage or tube 98, because the drawn air may result in a misdetection of the bead detector 100. However, this is not restrictive for the present invention and the separation unit may be partially immersed in the liquid.

Figs. 4 and 5 illustrates a bead separator according to the second embodiment of the present invention. The separator 110 includes a main portion or housing 112. The housing 112 has a cylindrical exterior in this embodiment, though; the present invention is not limited thereto. The housing 112 also has a cylindrical inner peripheral surface 113 defining therein an interior 114 in the form of cylinder, extending substantially horizontally from one side of the housing, for accommodating a cylindrical bead holder 116. The bead holder 116 has an outer diameter identical to or slightly less than the inner diameter of the cylindrical interior 114 of the housing 112, so that it can rotate within the interior 114 about its horizontal axis. At the rotation of the bead holder 116, it makes a frictional contact at its outer periphery 117

with the inner periphery 113 of the interior 114, which may wear both inner and outer peripheries, 113 and 117. For this reason, the housing 112 and bead holder 116 may preferably be made of wearproof materials to prevent both housing 112 and bead holder 116 from wearing by such contact. For example, in this embodiment, the housing 112 is made of stainless steel and the bead separator 116 of urea resin. Instead, either or both of the inner surface 113 of the housing 112 and the outer surface 117 of the bead holder 117 may be covered and protected with a slippery material, such as polytetrafluoroethylene.

An opening of the interior 114 is closed by a closure 118 which is releasably fixed to the housing 112 using a plurality of bolts 120 or other suitable fixing means. Preferably, the closure 118 as well as the housing 112 may be made of wearproof material for reducing possible wear of the bead holder 116 and the closure 118. Also, to minimize the wears of the closure 118 and bead holder 116, a surface of the closure 118, confronting to the bead holder 116, may be covered with a slippery material, such as, polytetrafluoroethylene.

The closure 118 has a through-hole 122 extending horizontally on the longitudinal axis of the bead holder 116. Also, the closure 118 supports a motor 124 so that a drive shaft 126 of the motor 124 is inserted in the

through-hole 122. The inserted drive shaft 126 is securely engaged in a hole 128 formed in a surface opposing to the closure 118 so that, by driving the motor 124, the bead holder 116 rotates at a certain speed in a direction indicated by an arrow 140. (see Fig. 4)

The bead holder 116 has a plurality of passages 130 in an intermediate cross-sectional plane, each of which extends radially from a portion spaced a certain distance away from the longitudinal axis of the bead holder to the outer periphery of the bead holder. In this embodiment, the bead holder 116 has six passages 130 spaced at regular angles of 60°, though; the present invention is not limited thereto. Also, the outer end of the passage 130 adjacent to the outer periphery 117 of the bead holder 116 is enlarged radially into a truncated cone, thereby forming a concaved portion or recess 132.

A depth of the recess 132 is determined so that, when the bead is received in the recess 132, the bead projects partially from the recess 132. Also, a diameter of a bottom portion of the recess 132, connected with the passage 130, is determined to be smaller than the bead size so that the bottom portion prevents the beard 134 from entering into the passage 130. Although the passage 130 has a constant cross-sectional area over its entire length, however; it is not restrictive to the present invention.

For example, it is sufficient that only a portion connecting the passage to the recess in the vicinity of the recess 132 may be smaller than the bead size and, in this instance, the remaining portion of the passage may be larger than the bead size.

The inward end of the passage 130 is further extended in parallel to the longitudinal axis of the bead holder 116 to the opposite end surface 136 away from the motor 124. (see Fig. 5) An inner surface portion 138 of the housing 112, confronting to the end surface 136 of the bead holder 116, is formed with a header or elongated groove 141 along an imaginary circle drawn by the confronting end of the passage 130 at the rotation of the bead holder 116. The elongated groove 141 draws an inversed-U shape when view from the bead holder 116. Also, the inner surface portion 138 of the housing 112 is formed with another header or shortened groove 142 on the imaginary circle between opposing ends of the elongated groove 141. The headers 141 and 142 are connected to passages 144 and 146, respectively. In turn, the passage 144 is connected to a suction pump 148 and the passage 146 to a supply pump 150.

As best shown in Fig. 4, an intermediate portion 152 of the housing 112, confronting to the recess 132, is formed with a hole 156 connecting between the interior and

exterior of the housing 112 for receiving a bead hopper 158. More specifically, the hole 156 is positioned in a region where each peripheral portion of the bead holder 116 rotating in the direction indicated by the arrow 140 moves past right before reaching the topmost position 154, i.e., in the region of about 10 to 11 o'clock in Fig. 4. Further, a nozzle 160 for connecting between the interior and exterior of the intermediate portion 152 is formed in a portion adjacent to the topmost position 154 but away from the hole 156, i.e., in the region of about one o'clock, confronting to the recesses 132 at the rotation of the bead holder 116. The nozzle 160 is further connected to a supply pump 162 for supplying the liquid into the interior of the housing 112. Furthermore, the inner periphery 113 of the intermediate portion 152 is formed with a groove or tunnel 164 connecting between the hole 156 and the nozzle 160. At the lowermost portion of the intermediate portion 152, an outlet 168 is formed for collecting beads transported by the recesses 132. The outlet 168 is extended from the interior to exterior of the intermediate portion 152. Also, an outer opening of the outlet 168 is connected to a tube 171 for receiving and then transporting the beads. The transporting tube 171 is equipped with a bead detector 170 for detecting bead using laser, for example, to be transported in the tube 171.

In addition, the inner periphery of the bead holder 116 is formed with a groove or tunnel 172 extending from the nozzle 160 to the outlet 168 adjacent to a pass along which the recesses move from the nozzle 160 to the outlet 168. A depth of the tunnel 172 is determined to be larger than the portion of the bead 134 possibly projected from the recess 132, so that the bead 134 retained in the recess 132 is prohibited from making any contact with the inner surface 113 of the intermediate portion 152.

In the operation of the separator 110 so constructed, similar to the first embodiment, the separator 110 is fully immersed in the liquid having a specific density slightly smaller than the bead 134, such as, ethanol. Also, the housing 112 is secured in the vessel not shown. The outlet of the suction pump 148 is connected to the bead hopper 158, and the inlet of the supply pumps 150 and 162 are positioned in the liquid. The bead hopper 158 is supplied with a number of beads 134 with liquid 174. As mentioned above, the specific gravity of the bead 134 is slightly greater than that of the liquid 174, allowing the beads 134 to exist adjacent to the bottom of the bead hopper 158, i.e., the outer periphery of the bead hopper 116.

When the motor 124 is driven to rotate the bead holder 116 in the direction of arrow 141. This causes each

inner end of the passages 130 to pass through the headers 141 and 142, alternately. More specifically, the headers 141 and 142 are formed in positions independently. Therefore, only when the passage 130 directs in the direction of six o'clock, the opposing end of the passage 130 confronts to the shortened header 142. Also, only when the passage 130 directs in the region from seven to five o'clock with respect to the clockwise direction, the passage 130 confronts to the elongated header 141.

In synchronism with the motor 124, the suction pump 148 and supply pumps 162 and 150 are energized. This causes that a negative pressure or suction is introduced by the suction pump 148 through the passage 144 and then the header 141 into the passage 130 confronting to the header 141. Contrary to this, a positive pressure is introduced by the supply pump 150 through the passage 146 and then the header 142 into another passage 130 confronting to the header 142. Also, the liquid 174 is supplied into the nozzle 160 by the supply pump 162.

Upon rotation of the bead holder 116, each recess 132 in the outer periphery 117 of the bead holder 116 moves past the retaining station A. In this station, since the inner end of the passage 130, the recess 132 holds one bead 134 therein due to the negative pressure generated in the passage 130 by the pump 148. At this moment, the recess

132 does not hold two or more beads therein because, as mentioned above, it is sized to receive only one bead 134 therein. However, one or more beads 134 can exist in the vicinity of the bead 134 retained in the recess 132.

Then, the recess 132 retaining the bead 134 therein advances into the tunnel 164, i.e., restricting station B where the liquid 174 is ejected from the nozzle to the bead or beads retained around the recess 132. This removes the bead or beads around the recess 132 away from the recess. On the other hand, the bead 134 retained in the recess 132 is positively held by the negative pressure in the recess 132.

As a result, only one bead 134 retained in the recess 134 is transported into the next tunnel 172 by the rotation of the bead holder 116. Since the opposite end of the passage 130 is still fluidly connected to the header 141, the bead 132 is held in the recess 132. Afterwards, in the position at five o'clock or so, the passage 130 leaves the header 141. Immediately after that, in the subsequent position at about six o'clock, the recess 132 and the associated one end of the passage 130 come to confront to the outlet 168 and the opposite end of the passage 130 to the header 142. Therefore, the liquid 174 supplied from the pump 150 flows through the header 142 into the passage 130, thereby the bead 134 is released out

of the recess 132 into the outlet 168. The bead 134 as well as liquid is then transported through the transporting tube 171 to the bead detector 170 where it is detected by the detector. Finally, the bead 134 is distributed into the corresponding well by a bead distributor in the combinatorial synthesizing process not shown. The recess 132 from which the bead 132 has been removed is then transported to the retaining station A again where the new bead 134 is separated from the group of beads and then held in the recess 132.

It should be noted that in the second embodiment the bead holder 116 is formed with the recesses 132 in one transverse sectional plane, through; it may be provided in a plurality of transverse sectional planes.

Further, although the bead separator 110 is fully immersed in the liquid, the present invention is not limited thereto.

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the sprit and scope of the invention.

CLAIMS

1. A separator for separating each bead from a group of beads preferably for use with a combinatorial synthesizing method and/or high-throughput cleaning process, comprising:

(a) a bead holder including

a surface having a recess sized to receive a single bead,

a passage connected at one end thereof to said recess, and

a restricting portion for preventing said bead from being entering into said passage;

(b) a first station for introducing a negative pressure in said passage, thereby holding said bead in said recess;

(c) a second station for ejecting a liquid around said recess retaining said bead, thereby removing a bead or beads possibly existing around said recess away from said recess;

(d) a third station for introducing a positive pressure in said passage, thereby releasing said bead from said recess; and

(e) a transporting means for moving said recess through said first, second, and then third stations.

2. A separator in accordance with claim 1, wherein said recess is in the form of truncated cone having a first opening away from said passage and a second opening adjacent to said passage, said second opening being sized to be smaller in diameter than said bead to form said restricting portion.

3. A separator in accordance with claim 1, wherein said recess is in the form of cylinder, and said bead holder further comprises a filter positioned between said recess and said passage for preventing said bead from entering into said passage.

4. A separator in accordance with claim 1, wherein said recess has a depth smaller than a size of said bead so that a portion of said bead protrudes from said recess.

5. A separator in accordance with claim 1, further including a member, said member including a groove extending adjacent to a pass along which said recess moves past said second to third stations, said groove having a depth smaller than a size of said bead so that said protruded portion of said bead moves in said groove.

6. A separator in accordance with claim 1, wherein said bead holder and said first to third stations are substantially immersed in said liquid.

7. A separator for separating each bead from a group of beads preferably for use with a combinatorial

synthesizing method and/or high-throughput cleaning process, comprising:

an axis;

a bead holder rotatably mounted about said axis, said bead holder having a recess sized to receive a single bead, a passage fluidly connected to said recess, and a restricting portion for preventing said bead from entering into said passage;

a motor for rotating said bead separator about said axis so that said recess of said bead separator moves along a circular pass;

a first station positioned adjacent to said circular pass, said first station having a first chamber for receiving said group of beads and means for introducing a negative pressure in said passage when said recess is moving past said first station and, thereby, holding said bead in said recess;

a second station positioned adjacent to said circular pass and subsequent to said first station, said second station having means for keeping said negative pressure in said passage and a nozzle for ejecting a fluid adjacent to said recess and, thereby, removing a bead or beads possibly existing around said recess away from said recess; and

a third station positioned subsequent to said

second station and adjacent to said circular pass, said third station having means for introducing a positive pressure in said passage for releasing said bead from said recess.

8. A separator in accordance with claim 7, further comprising a tube for transporting said bead released from said recess at said third station, said tube being equipped with a detector for detecting said bead to be transported in said tube.

9. A separator in accordance with claim 7, further comprising a first pump, fluidly connected with said passage, for introducing said negative pressure in said passage at said first and second stations.

10. A separator in accordance with claim 7, further comprising a second pump, fluidly connected with said nozzle, for supplying said fluid to said nozzle at said second station.

11. A separator in accordance with claim 7, further comprising a third pump, fluidly connected with said passage, for introducing said positive pressure in said passage at said third station.

12. A separator in accordance with claim 7, wherein said means for introducing said negative pressure in said first station and keeping said negative pressure at said second station includes a member having a suction chamber

which extends from where an opposite end of said passage positions when said recess is moving past said first station to where said opposite end of said passage positions when said recess is moving past said second station, and a suction pump for introducing said negative pressure through said suction chamber to said passage.

13. A separator in accordance with claim 7, wherein said bead holder is in the form of disc, and said recess is formed in a major surface of said disc.

14. A separator in accordance with claim 7, wherein said bead holder is in the form of cylinder, and said recess is formed in an outer periphery of said bead holder.

15. A method for separating each bead from a group of beads preferably for use with a combinatorial synthesizing method and/or high-throughput cleaning process, comprising the steps of:

(a) providing a bead holder having a recess sized to receive a single bead, a passage fluidly connected with said recess, and a restricting portion for preventing said bead from entering into said passage;

(b) introducing a negative pressure in said passage, thereby receiving said bead in said recess;

(c) ejecting a liquid around said recess retaining said single, thereby removing a bead or beads possibly existing around said recess away from said recess;

(d) introducing a positive pressure in said passage, thereby releasing said bead from said recess.

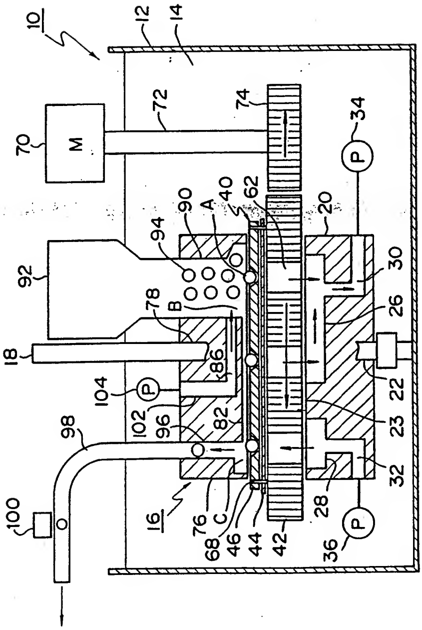
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Fig. 1

Fig. 2

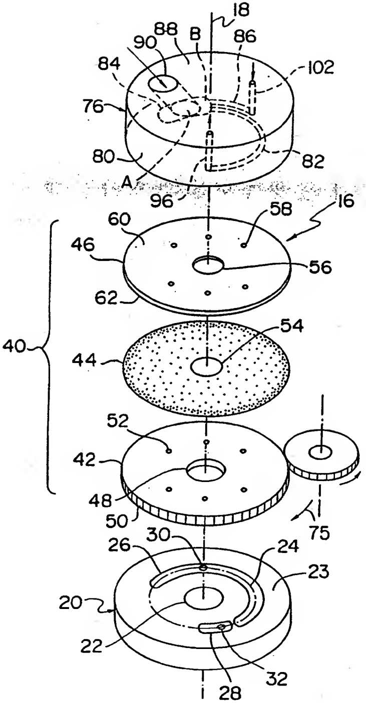
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Fig. 3

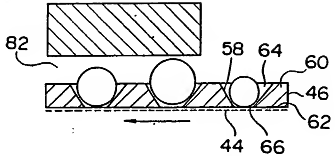
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Fig. 4

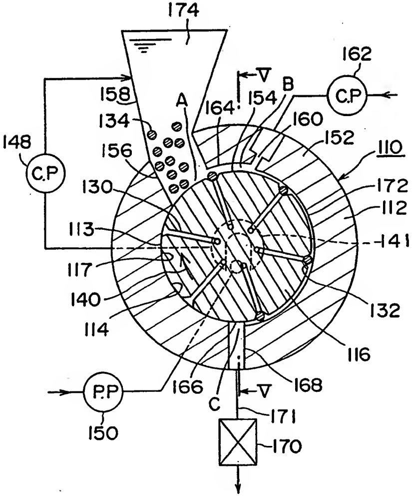
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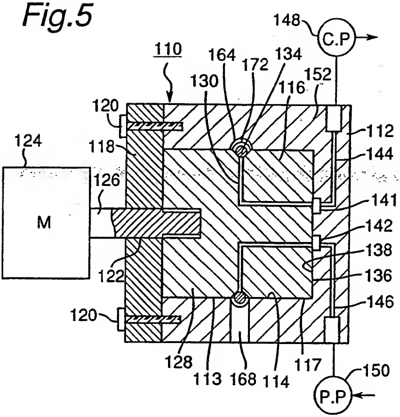
Fig.5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P.P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 99/00707

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J19/00 B01J4/02 B01L11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01J B01L B07C G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 17258 A (GLAXO GROUP LIMITED) 15 May 1997 see page 1, line 14 - line 18 see page 2, line 15 - page 4, line 8 see page 9, line 8 - line 26 see page 11, line 1 - page 13, line 21 see figures 1-10	1-12,15
P,A	WO 98 24549 A (SMITHKLINE BEECHAM PLC) 11 June 1998 see the whole document	1-14
A	US 4 937 048 A (MASAHIKO SAKAI ET AL.) 26 June 1990 see abstract see column 5, line 18 - column 6, line 5 see figures 6-8	1,5, 7-11,13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search	Date of mailing of the international search report
26 May 1999	04/06/1999

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 91 06496 A (AUTOTROL CORPORATION) 16 May 1991 see abstract; figures	1,7,13, 14
A	WO 94 28119 A (SMITHKLINE BEECHAM P.L.C.) 8 December 1994	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 99/00707

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WO 9717258 A	15-05-1997	US 5722470 A	03-03-1998
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